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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1632	9

DATE MAILED: 11/14/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

FILE

Office Action Summary

Application No.	Applic
09/427,657	Alltalo et al.
Examiner	**Group Art Unit**
Gai (Jennifer) Mi Lee	1632

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is clos d** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-30* is/are pending in the applicat

Of the above, claim(s) *19, 20, and 22-28* is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-18, 21, 29, and 30* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Applicant's election with traverse of Group I, claims 1-18, 21 and 29-30 filed August 10, 2000 in Paper No. 7 is acknowledged. The traversal is on the ground(s) that the claims of Group I/III and II/IV are related in that the polynucleotides recited in the claims of Group I/III encode the polypeptides recited in the claims of Group II/IV. Applicants argue that the Patent Office has classified both Group I/III and II/IV in class 514 indicating that the patentability searches that the Examiner will conduct for these groups are likely to be co-extensive, and thus, weighs against division of these groups of claims. This is not found persuasive because the Groups I/III are biologically and chemically distinct, unrelated in structure and function, made by and used in different methods from that of Groups II/IV. Therefore, the restriction groups have acquired a separate status in the art as a separate subject for inventive effect and require independent searches. A reference which would anticipate the invention of one group would not necessarily anticipate or make obvious any of the other groups. Moreover, as to any question regarding the serious burden of search, classification of subject matter is merely one indication of the burdensome nature of the search involved. While the two groups are both classified in class 514, they are separate subclass thus, the literature search between different groups, particularly relevant in this art, is not co-extensive.

After careful review and reconsideration of election/restriction, the examiner has decided to rejoin Group I and III as a single invention drawn to a medical device and a method of treating restenosis or stenosis comprising a polynucleotide encoding VEGF-C and VEGF-D. Group II

and IV are also rejoined as a single invention drawn medical device and a method of treating restenosis or stenosis comprising a polypeptide of VEGF-C and VEGF-D which is biologically and chemically distinct, unrelated in structure and function, made by and used in different methods from Group I and III. Thus, Groups I and III are not required for any of the method of Groups II and IV.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-18 and 21-30 are currently pending.

Claim Objections

Claims 22-30 are objected to because of the following informalities: Claims 22-30 are objected to for embracing non-elected subject matter. Applicant should amend the claims to reflect the above election. Appropriate correction is required.

Information Disclosure Statement

The information disclosure statement filed August 24, 2000 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered.

The information disclosure statement filed August 24, 2000 fails to comply with 37 CFR 1.98(a)(1), which requires a list of all patents, publications, or other information submitted for

consideration by the Office. It has been placed in the application file, but the information referred to therein has not been considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-18 and 21-30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The factors to be considered have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex Parte Forman*, (230 USPQ 546 (Bd Pat. App. & Int. 1986)).

The claims are drawn to a method of treating a mammalian subject to prevent stenosis or restenosis of a blood vessel, comprising the step of : administering to a mammalian subject in need of treatment to prevent stenosis or restenosis of a blood vessel a composition comprising a polynucleotide said polynucleotide comprising a nucleotide sequence that encodes a vascular endothelial growth factor C or D (VEGF-C or VEGF-D) polypeptide, thereby preventing stenosis or restenosis of said blood vessel (claim 1 and 21) and a medical device designed to contact a

surface of a blood vessel in the course of surgery to treat stenosis of the blood vessel, comprising integrating into the device a composition effect to prevent restenosis, said composition comprising at least one anti-restenosis agent such as VEGF-C or VEGF-D polynucleotide (claim 22).

The claims are not enabled as the specification does not provide guidance as to preventing restenosis or stenosis, promoters to regulate expression, modes of delivery to supply effective prevention of restenosis or stenosis of a blood vessel in a mammalian subject (addressed in detail below).

The claimed methods and products are directed to gene therapy, which has proved to be a highly unpredictable art. The realities of the parameters which will result in therapeutic benefit have not been achieved. The achievement of therapeutic results by gene therapy, the art as a whole found this to be unpredictable. Eck & Wilson (The Pharmacological Basis of Therapeutics, 1996) teach numerous factors complicate the gene delivery art which would not have been shown to be overcome by routine experimentation. These include, the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ

dramatically based on the vector used and the protein being produced, which cells are target cells, and the disease and/or host being treated.

With regard to VEGF-C as a growth factor for blood vascular endothelial cells, Enholm et al (1998), Trends in Cardiovascular Medicine 8/7: 292-297, teach that the major questions about the biological roles VEGF-C are not answered yet and that it is not known how important the potential of mature VEGF-C to induce proliferation of blood vessels via the VEGFR-2 is in various conditions. Enholm et al further question how the proteolytic processing of VEGF-C regulated in vivo and does VEGF-C regulate the permeability of lymphatic vessels as well as the blood vessel? Enholm et al teach that experiments using purified recombinant proteins and different molecular genetic approaches including gene targeting are crucial on VEGF-C function (page 296, column 1).

The claimed invention (claims 1-18, 21-25 and 29-30) embraces administering a polynucleotide encoding VEGF-C or D in a mammalian hosts to prevent stenosis or restenosis of the blood vessel with a kit or in a medical device. **Note** that prevention encompasses complete amelioration of symptoms associated with restenosis/stenosis or cure of restenosis/stenosis and not necessarily mere enhancement of vascular permeability and promotion of angiogenesis. In the Examples, the specification discloses an *in vivo* rabbit restenosis model, demonstrating the efficacy of adenovirus-mediated intravascular VEGF-C gene transfer for inhibiting post-angioplasty restenosis (Example 1, page 25). Viral titer of 1.15×10^{10} pfu was administered to each New Zealand White rabbit using a channel balloon local drug delivery catheter into the left

renal artery, in a segment free of side branches, via a 5F percutaneous introducer sheath in the right carotid artery and inflated to 6 ATM for 10 minutes (page 27). Gene transfer efficiency was evaluated using X-GAL staining of OCT-embedded tissues. Histological analysis revealed that *lacZ* (control) had an I/M (Intima/Media as parameter for intimal thickening) ratio of **0.61** two weeks after gene transfer from the VEGF-C transfected groups of I/M ratio of **0.40** in which the VEGF-C group had a **smaller** I/M ratio persisted at 4 weeks time point after gene transfer (page 28). Example 5 discloses the use of naked VEGF-C transgene with a hydrogel-coated balloon catheter delivery (page 34-35). Examples 6 and 7 disclose using stent to deliver concurrently or immediately before or after implantation to **inhibit** neointimal thickening and/or decreased thrombotic occlusion in the VEGF-C gene-treated animals versus control animals or an extravascular collar implanted around the carotid arteries of New Zealand White Rabbits (page 35). However, the specification fails to teach the level of VEGF-C or D gene function necessary to achieve prevention such as complete amelioration of symptoms associated with restenosis/stenosis of a blood vessel in any mammalian subject as opposed to reducing or inhibiting restenosis or stenosis. While the examples show that administration of the VEGF-C gene reduced the degree of stenosis relative to controls, the results show no evidence that stenosis was prevented by the expression of VEGF-C.

The specification further fails to address how to overcome expression of VEGF-C or VEGF-D without an appropriate promoter such that one would be able to express VEGF-C or VEGF-D in target cells in a subject to prevent restenosis or stenosis of a blood vessel. In the

Examples, the specification disclose an adenovirus plasmid containing a cDNA encoding the complete human prepro-VEGF-C open reading frame operably linked to a cytomegalovirus (CMV) promoter and human growth hormone polyadenylation signal sequence (page 26). However, claims 1 and 21 did not recite a promoter operably linked to the polynucleotide encoding VEGF-C or VEGF-D, specifically. As such, the claims encompass administering a gene without a promoter and the specification fails to teach a specific purpose of administering the polynucleotide encoding VEGF-C or VEGF-D without expression that would be effective in treating or preventing restenosis or stenosis.

As for the route of administration, Applicant's specification fails to provide guidance to the skilled artisan on the parameters for gene delivery (targeting) for the breadth of the claimed invention. Applicant's claims (claims 1-18 and 21) embrace any and all routes of administration with a polynucleotide encoding VEGF-C or VEGF-D such as systemic delivery. However, the specification only teach a direct delivery of the polynucleotide or in a medical device such as a catheter to the location of the target cells to inhibit restenosis or stenosis. While progress has been made in recent years for *in vivo* gene transfer, vector targeting *in vivo* to desired locations continues to be unpredictable and inefficient. This is supported by numerous teachings available in the art. For example, Miller et al. reviews the types of vectors available for *in vivo* gene therapy, and conclude that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances...targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of

safe and highly efficient delivery systems" (page 198, column 1). Deonarain is a 1998 publication which indicates that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise, but is currently even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma et al. (published in 1997) reviews various vectors known in the art for use in gene therapy and the problems which are associated with each and clearly indicated that at the time of the claimed invention resolution to vector targeting had not been achieved in the art (see entire article). Verma also indicates that appropriate enhancer-promoter sequences can improve expression, but that the "search for such [useful] combinations is a case of trial and error for a given cell type" (page 240, sentence bridging columns 2 and 3). Crystal also reviews various vectors known in the art and indicates that "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (page 409). With regard to arterial wall gene transfer, Laitinen et al (1998) Pharmacological Res., Vol. 37(4): 251-254, teach that a major problem in the intra-arterial gene transfer is that endothelium and internal elastic lamina form physical barriers that limit penetration of gene transfer vectors into the arterial wall, plasma interferes with all gene transfer methods and the systemic leakage of the gene transfer vector is more likely in intravascular approaches. Furthermore, gene transfer efficiency using intravascular delivery of plasmid-

liposome complexes and retroviruses has also been very low (page 251, column 1). Turunen et al (1999), Exp. Gerontol., Vol. 34 (4): 567-574, further support Laitinen et al in teaching that restricted local delivery via intravascular route may not be possible due to leakage of the gene transfer solution in systemic circulation which could result in the expression of transgene in undesired locations (page 570).

Thus, the cited prior and post-filing art clearly indicates an unpredictable status of the gene therapy art and effective treatment to prevent restenosis or stenosis. And, although, specific vectors, promoters, genes, and routes of administration might be or may have been effective for treatment of a specific disease (i.e., restenosis) providing a specific therapeutic effect, gene therapy as a broad-based art is clearly unpredictable in terms of achieving levels and duration of expression of a gene of interest which results in a therapeutic effect. As the claims are not limited to any specific embodiment of gene therapy with the breadth of the claims is drawn to a method of administering by any and all routes of a polynucleotide comprising a nucleotide sequence that encodes a vascular endothelial growth factor C or D polypeptide for preventing stenosis or restenosis of said blood vessel in any and all subject via gene therapy. However, it appears from the teachings of the post-filing art, that several parameters of the claimed invention are critical to achieving such treatment, particularly, complete prevention of restenosis or stenosis, promoters to regulation gene expression and route of delivery need to be addressed.

Accordingly, in view of the quantity of experimentation necessary to determine the parameters for achieving prevention of restenosis or stenosis with a method of any and all routes

administering a polynucleotide encoding a vascular endothelial growth factor C or D polypeptide in any and all subject via gene therapy, the lack of direction or guidance provided by the specification with regard to achieving complete prevention of restenosis or stenosis without addressing promoter regulated gene expression and route of administration for gene therapy in any and all subject, and the breadth of the claims, it would have required undue experimentation of one skilled in the art to make and/or use the claimed invention as broadly claimed.

The above rejection could be overcome by amending all claims to recite that stenosis or restenosis is inhibited rather than "prevented". All claims should further recite operable linkage of a promoter to the VEGF-C/D coding sequence where the promoter is functional in the intended target cells, and method claims should limit route of administration to direct application of the vector to the target cells.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-17 and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 21 are incomplete. While all of the technical details of method need not be recited, the claims should include enough information to clearly and accurately describe the

invention and how it is practiced. The method of claims 1 and 21 are missing process steps. The method step needs to relate back to the preamble because it is unclear how mere administration without expression correlates to treating a mammalian subject to prevent stenosis or restenosis of a blood vessel. **Note**, claims 2-17 depend from claim 1.

Conclusion

Claims 1-18 and 22-30 appear to be free of the cited prior art of record because the cited prior art of record fails to teach or suggest a kit, a device or a method for preventing restenosis or stenosis by administering to a mammalian subject in need of treatment to prevent stenosis or restenosis of a blood vessel a composition or a medical device designed to contact a surface of a blood vessel in the course of surgery to treat stenosis of the blood vessel comprising a polynucleotide, said polynucleotide comprising a nucleotide sequence that encodes a VEGF-C or VEGF-D.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Note that applicants should keep these prior art in mind when amending their claims.

Isner (U.S. Patent #5,830,879).

Isner discloses a method for inducing reendothelialization of the lining of an injured blood vessel comprising contacting the injured portion of the vessel with nucleic acid encoding

an endothelial cell mitogen such as vascular endothelial growth factor operably linked to a promoter to result in expression of the mitogen when delivered to the cells at the site of vascular injury (abstract). Isner further discloses a method of inducing reendothelialization in injured blood vessel in a human host comprises a denuded portion of its endothelial lining by administering to cells of said injured vessel in the human host an effective amount of DNA that encodes VEGF admixed with an hydrogel polymer and expressing the VEGF wherein the blood vessel injury is the result of balloon angioplasty or the deployment of an endovascular stent, concurrently with angioplasty to reduce restenosis in a human host (See claims). Isner discloses that the DNA may also be used with a microdelivery vehicle such as cationic liposome and replication-defective recombinant adenoviral vectors (column 6, 2nd-3rd paragraph) and catheter-mediated transfer of such delivery vehicles into the percutaneous transluminal arteries. Witzenbichler et al (Aug 1998) American Journal of Pathology, Vol. 153 (2): 381-94.

Witzenbichler et al disclose an *in vivo* administration of a naked plasmid DNA (pcVECF-C; 500ug) from the polymer coating of an angioplasty balloon by direct intra-arterial infusion which showed evidence of therapeutic angiogenesis for both pcVEGF-C and rhVEGF-C (abstract). Witzenbichler et al further disclose that VEGF-C and its receptors may represent an alternative to VEGF-A for strategies of therapeutic angiogenesis in patients with limb and/or myocardial ischemia (abstract). Witzenbichler et al teach that when administered in vivo as plasmid DNA or recombinant protein, VEGF-C was shown to enhance vascular permeability and promote angiogenesis in a rabbit model (page 382, column 1, 4th paragraph). Witzenbichler et al

further teach a percutaneous arterial gene transfer of pcVEGF-C using a 2.0-mm hydrogel-coated balloon catheter into the internal iliac artery of the ischemic limb (page 384, column 1-2).

Achen et al (WO 98/07832).

Achen et al disclose the use of VEGF-D for stimulating endothelial cell proliferation and angiogenesis and increases vascular permeability

Joukov et al (1996), EMBO Journal, Vol. 15 (2): 290-298.

Joukov et al disclose 100% of the sequence modifications of SEQ ID NO: 2. Joukov et al further disclose that pREP7 expression vector transfected into 293 cells in which VEGF-C was secreted by transfected cells (page 298, Materials and Methods).

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gai (Jennifer) Mi Lee, whose telephone number is 703-306-5881. The examiner can normally be reached on Monday-Thursday from 8:30 to 5:00 (EST). The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached on 703-305-6608. The FAX phone numbers for group 1600 are 703-308-4242 and 703-305-3014.

An inquiry of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is 703-308-0196.

Gai (Jennifer) Lee
Patent Examiner
Art Unit 1600

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER